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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/223,634	12/31/98	NOELLE	R 012712-652

EXAMINER

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HM12/0607

ART UNIT	PAPER NUMBER
~~GAMBEL, P~~ 1644 1644	8

DATE MAILED: 06/07/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 3/20/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1, 2, 4-10 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1, 2, 4-10 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☑ The proposed drawing correction, filed on 12/31/98 is ☑ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1998-404-496/40517

DETAILED ACTION

1. Applicant's election of the species gp39-specific antibodies and diabetes of in Paper No. 7, filed 5/20/00 is acknowledged.

Claim 11 has been canceled. Claim 3 has been canceled previously
Claims 1,2 and 4-10 are pending and being acted upon.

2. Formal drawings have been submitted which comply with 37 CFR 1.84.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. The Abstract of the Disclosure does not adequately describe the claimed invention..

5. Applicant should amend the first line of the specification to update the status of the priority documents. USSN 08/481,735 is now U.S. Patent No. 5,833,987.

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

"BALB/c" is the proper designation of this mouse strain.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

7. Claims 1,2, and 4-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

A) Claims 1, 2 and 4: Antagonist of a Receptor on a Surface of T Cell which Mediates Contact Dependent Helper Effector Functions.

The instant claims encompass and are broadly drawn to antagonist of a receptor on a surface of T cell which mediates contact dependent helper effector functions; which encompass various antagonists or molecules capable of inhibiting interaction between gp39 (CD40 ligand) and cells as well as a myriad of T cell surface receptors.

However, there is insufficient direction and guidance as to the structure or specificity or objective evidence to support the inhibition of the interaction between CD40 ligand and cells for the claimed methods; other than the gp39/CD40L specificity and the use of gp39-/CD40L-specific antibodies.

For example, the claimed antagonists encompass a myriad of antagonists including antibodies, proteins, non-protein molecules which may inhibit the interaction of T cell helper molecules or gp39/CD40 ligand and cells via a mechanism that does not involve gp39/CD40 ligand. Aslo, inorganic compounds or drugs may inhibit T cell helper function including gp39/CD40 ligand interactions, but the absence of guidance in the specification with regard to screening for or designing the appropriate antagonists renders the identity of such antagonists unpredictable. The specification provides no support for such inhibitory processes and provides no guidance to direct the skilled artisan to identify the various molecules encompassed by the claimed methods which might affect such uncharacterized processes. Further, the broadly claimed antagonists encompass a variety of molecules, which may or may not be antibody or protein based.

In addition, there is insufficient guidance and direction in the specification for targeting antagonists to any receptor on a surface of a T cell which mediates contact dependent helper effector functions. There are a myriad of T cell markers and applicant has not defined nor provided objective evidence that would indicate that targeting any antagonist against any T cell marker would result in treating a T cell mediated disorder.

For example, Bach (TIPS, 14: 213-216, 1993) discusses the limitations of immunosuppressive therapy of autoimmune diseases with antibodies directed against T cells (see entire document). Although there has been some success with CD4 in psoriasis and perhaps arthritis, Bach clearly indicates that autoimmune disease cannot be considered as a whole and treatment selection must be considered with each disease (page 213, column 3). Also T cell intervention does not have the same sensitivity in each disease. Bach also reviews the art-known resistance of autoimmunity to therapeutic intervention (page 215, column 3).

Additionally, all the claimed methods encompass in vivo administration of a number of antagonists and T cell helper molecules, and as it has been well known to the skilled artisan that dosage parameters and administration protocols vary from molecule to molecule depending on clearance and reactivity of the molecule/antagonist with internal factors. Therefore, in view of the breadth of the claims and the unpredictability in the art, and in view of the insufficient guidance and working examples in the specification, the quantity of experimentation required by one skilled in the art to practice the invention undue.

B) Claims 1,2, and 4-10: Treating T Cell Mediated Human Autoimmune Disorders.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs or biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vitro experimental observations and limited animal models using gp39-specific antagonists accurately reflects the relative ability of gp39-specific antagonist such as gp39-specific antibodies to inhibit the autoimmune diseases, particularly as they read on human autoimmune diseases, encompassed by the claimed methods.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively inhibit human autoimmune diseases such as diabetes, oophoritis and thyroiditis in a human. The specification does not teach how to extrapolate data obtained from in vitro experimental assays and limited animal models o the development of effective in vivo methods to inhibit autoimmune diseases, commensurate in scope with the claimed invention.

In contrast to acute conditions, the chronic and complicated nature of the targeted disorders encompassed by the claimed methods are diagnosed only after significant tissue damage has occurred and/or have an ongoing immune response.

Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol., 1992; see entire document, particularly page 558, column 2)(1449, of record).

Bach (TIPS, 14: 213-216, 1993) discusses the limitations of immunosuppressive therapy of autoimmune diseases with antibodies directed against T cells (see entire document). Although there has been some success with CD4 in psoriasis and perhaps arthritis, Bach clearly indicates that autoimmune disease cannot be considered as a whole and treatment selection must be considered with each disease (page 213, column 3). Also T cell intervention does not have the same sensitivity in each disease. Bach also reviews the art-known resistance of autoimmunity to therapeutic intervention (page 215, column 3).

With respect to treating various inflammatory conditions with CD40-CD40 ligand antagonists in the face of an ongoing or established immune response, the following limitations have been noted.

Gray et al. (J. Exp. Med. 180: 141-155, 1994) teaches that the secondary response was not readily blocked by sCD40-γ1 treatment, indicating a relative independence of CD40 ligation of antigen-experienced B cells (see entire document, including Abstract). Here, if sCD40-γ1 were delayed until day 4 of the primary response, mice develop normal and possibly enhance memory responses.

In addition, Stuber et al. (J. Exp. Med. 183: 693-698, 1996) teaches when ant-gp39 was given after the disease was established, no effect on the disease activity was observed (see entire document, including Abstract and Discussion). Here, Stuber et al. distinguishes between treating acute conditions such as transplant rejection versus chronic conditions such as autoimmune diseases (see Discussion, last paragraph).

Biacone et al. (Kidney Int. 48: 458-468, 1995) teach that soluble CD40 fusion protein can inhibit antibody-mediated glomerular disease if provided in a narrow window of early immune response but that this antagonist was not effective in reversing established disease (see entire document, including the Discussion, particularly the last two paragraphs).

Also, Resetkova et al. (Thyroid 6: 267-273, 1996) discloses observations on a model to determine the role of interactions between gp39 and CD40 in an established human Graves' disease and showed immunosuppressive effects on humoral response by directly blocking CD40-gp39 interactions in vivo (see entire document). However, this reference also clearly recognizes the limitations of such experimental observations by stating that it is not clear how anti-gp39 would function in an individual with Graves' disease with an intact immune system (page 272, column 2, paragraph 1)

Further a Press Release from IDEC Pharmaceuticals, Inc. (4/20/00) indicates that treating SLE with an anti-CD40L antibody based upon the claimed gp39-specific antibodies was not significantly different from that observed in the control group where a marked placed effect was noted and, in turn, the Phase III Development program will not be pursued at this time.

In addition two Biogen Press Releases indicating the halting of ongoing clinical trials, including its application to Factor VIII inhibitor syndrome, transplantation, multiple sclerosis, ITP and lupus nephritis, with Antova, which is another humanized CD40L- (or gp39-specific) antibody.
Similarly, Seachrist (BioWorld Today 10 (204) : 1,3, 10/25/99) discloses the halting of clinical trials using the humanized CD40-ligand specific antibody Antova. It is noted that this article discloses that a biotech analyst believes that Antova is dead in its present form.

Therefore, the reliance upon observations wherein the CD40-CD40 ligand antagonists are administered at the same time as initial stimulus or insult may inhibit certain T cell helper-mediated functions or interactions. Even though subsequent secondary responses may be affected, such observations still rely upon inhibiting activation of T cells at the onset or initiation of experiencing the antigen or stimulus and not upon experiencing an ongoing responses wherein secondary responses or antigen experienced lymphocytes are already in place. In contrast the claimed methods encompass using gp39-/CD40L--specific antibodies to treat autoimmune diseases wherein the diagnosis of such diseases occur after antigen priming has occurred.

CD40-CD40 ligand antagonists appear to inhibit the onset or activation of the immune response. In contrast, CD40-CD40 ligand antagonists do not appear to inhibit an established or ongoing immune or inflammatory responses, encompassed by the claimed methods, as evidenced by the references of record and set forth herein.

Therefore, it is not clear that the skilled artisan could predict the efficacy of the gp39-/CD40L-specific antibodies, as disclosed in the specification as filed to inhibit autoimmune diseases.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective antibody-based therapies on inhibiting human autoimmune diseases; undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent a sufficient number of working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting human autoimmunity with gp39-specific antibodies.

8. Claim 8: It is apparent that the 24-31 and 89-76 antibodies are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines / hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

Given the patented claims of U.S. Patent No. 5,747,037; these antibodies are considered enabled under 35 USC 112, first paragraph, for the deposit of biological materials.

9. Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is indefinite in the recitation of "chimeric" because the metes and bounds of said "chimeric" antibody is unclear and ambiguous. It is unclear whether "chimeric" refers to any recombinant antibody construct or to a particular antibody construct. For example, the art distinguishes "chimeric" antibodies as referring to variable (e.g murine) region - constant region (e.g. human) constructs, from "humanized" antibodies as referring to CDR-grafted antibodies

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

11. Claims 1 and 2 are rejected under 35 U.S.C. § 102(e) as being anticipated by Cobbold et al. (U.S. Patent No. 6,056,956). Cobbold et al. Teach treating autoimmune diseases such as rheumatoid arthritis or multiple sclerosis with CD4-specific antibodies (see entire document, including Claims). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods employing CD4-specific antibodies.

12. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1 and 4-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 5,833,947. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are drawn to a species of treating autoimmunity with gp39-specific antibodies, encompassed by the instant claims.

Claims 1 and 4-10 are directed to an invention not patentably distinct from claims 1-2 of commonly assigned U.S. Patent No. 5,833,947 for the reasons above.

Commonly assigned U.S. Patent No. 5,833,947, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78© to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

It is noted that the instant application names Noelle as the sole inventor; while U.S. Patent No. 5,833,947 names Noelle and Classen as inventors.

14. Claims 1,2 4-10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12 and 16-20 of copending application USSN 09/080,349. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims are drawn to a species of treating autoimmunity with gp39-specific antibodies, encompassed by the instant methods.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1,2 4-10 are directed to an invention not patentably distinct from claims 12 and 16-20 of commonly assigned USSN 09/080,349 for the reasons above. .

Commonly assigned USSN 09/080,349, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78© to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

It is noted that the instant application names Noelle as the sole inventor; while copending USSN 09/080,349 names Noelle and Classen as inventors.

15. The claimed methods of treating T cell mediated autoimmune disorders with gp39- (CD40L-specific) antibodies appear free of the prior art.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
June 6, 2000